Large number of receptors reduces cellular response time variation

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***Short Abstract* — Cells often have tens of thousands of receptors, even though only a few activated receptors can trigger full cellular responses. The reason for the overabundance of receptors is unknown. We suggest that the large number of receptors results in a reduced variability of the time to activation of the first few receptors out of many, and hence in a more synchronous activation of cells. We argue that, in simple models, this variability reduction does not interfere with the receptor specificity to ligands achieved by the Kinetic Proofreading mechanism. Thus cells can activate accurately in time and specifically to certain molecular signals.**

***Keywords* — spare receptors, kinetic proofreading, first passage time**

I. Introduction

Molecular signaling pathways that mediate cellular responses to changes in the surrounding world are often triggered by activation of cell surface receptors. For some such receptor-initiated signaling pathways (such as the T-cell or the estrogen receptor pathways), a handful of activated receptors can lead to a large cellular response. On the other hand, the number of receptors on a cell's surface may be tens to hundreds of thousands. Functional importance of this overabundance of ("spare") receptors is not understood. Elucidating the effects of the large number of receptors on the properties of signal transduction is our main goal.

We model a receptor state space as a linear chain of L states. Ligand presentation starts the progression along the chain, and reaching the final state in the chain leads to receptor activation. Kinetic proofreading (KPR) may be added to improve specificity of the receptor, and it is modeled by catastrophic events that return the system to the starting point with a certain rate [1,2]. The cell has $N >> 1$ receptors. While all of these receptors start their progression along the activation chain at about the same time, the cell is considered activated when only the first $1 \le m << N$ receptors reach their individual active states.

II. Results

For a model without kinetic proofreading, the time to activation of the first receptor out of many is given by the Weibull distribution, which has the coefficient of variation of $\sim 1/L$. When $m << N$ receptors are needed for the activation, the coefficient of variation further decreases to $\sim 1/(L\sqrt{m})$. Hence this "activation by the fastest" mechanism results in a dramatic reduction of the activation time variation.

Kinetic proofreading working in the regime of increasing specificity typically leads to an exponential activation time distribution for a single receptor [3]. This prevents the variance reduction by the activation by the fastest mechanism. Nonetheless, for biologically realistic parameter values, we show that receptors with the proofreading kinetics may be made to complete in an exponential time only if bound to an erroneous ligand, and in a narrower distributed time if bound to a correct ligand. The activation by the fastest mechanism then allows to have receptors that are highly specific (that is, trigger predominantly on a correct ligand), and yet temporally precise, with the activation time coefficient of variation of about $\sim 1/(L\sqrt{m})$.

III. Conclusion

We suggest that the large number of surface receptors may be employed by cells to significantly reduce the coefficient of variation and the mean completion time when triggered by a cognate ligand. This may be particularly important in the immune system, where synchronous immune cell activation may lead to a more efficient host response to pathogen invasions.

References

[1] Hopfield,J, *Proc. Natl. Acad. Sci. U.S.A.* **71**, 4135 (1974)
[2] Mckeithan T, *Proc. Natl. Acad. Sci. U.S.A.* **92**, 5042 (1995).
[3] Munsky B, Nemenman I, and Bel G, *J. Chem. Phys.* **131**, 235103 (2009).

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